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(54) Title: MEANS FOR DETECTING AND TREATING PATHOLOGIES LINKED TO FGFR3		
(57) Abstract The invention relates to a method for detecting carcinomas in a biological sample, comprising identifying FGFR3 mutations.		

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Means for detecting and treating pathologies linked to FGFR3

5

The invention relates to means, i.e. method and drugs, for detecting and treating, respectively, pathologies linked to FGFR3 and/or to the FGFR3 pathway.

Fibroblast growth factor receptor 3 (FGFR3) belongs to a family of
10 structurally related tyrosine kinase receptors (FGFRs 1-4) encoded by four different genes. These receptors are glycoproteins composed of two to three extracellular immunoglobulin (Ig)-like domains, a transmembrane domain and a split tyrosine-kinase domain. Alternative mRNA splicing results in many different receptors variants. Isoforms FGFR3-IIb and FGFR3-IIc result from a mutually exclusive splicing event in
15 which the second half of the juxtamembrane Ig-like domain is encoded either by the 151 nucleotides long exon 8 (IIb variant) or the 145 nucleotides long exon 9 (IIc variant).

Specific point mutations in the *FGFR3* gene which affect different domains of the protein are associated with autosomal dominant human skeletal disorders such as hypochondroplasia, achondroplasia, severe achondroplasia with developmental
20 delay and acanthosis nigricans and thanatophoric dysplasia. Several reports have demonstrated that these mutations lead to constitutive activation of the receptor. Taking into account this result, together with the skeletal overgrowth observed in mice homozygous for null alleles of *Fgfr3*, FGFR3 appears as a negative regulator of bone growth.

25 In contrast with this inhibitory role, an oncogenic role has been proposed for *FGFR3* in multiple myeloma (MM) development. In this malignant proliferation of plasma cells, a t(4;14)(p16.3;q32.3) chromosomal translocation with breakpoints located 50 to 100 Kb centromeric to *FGFR3* is present in 20-25% of the cases and is associated with overexpression of FGFR3.

30 In very rare cases (2 out of 12 MM cell lines and 1 out of 85 primary MM tumours), activating mutations of *FGFR3* previously identified in human skeletal disorders have been found, but always accompanied by the t(4;14)(p16.3;q32.3) translocation.

35 By investigating various cancers, the inventors have surprisingly found a role for FGFR3 in solid tumours, in particular in cancers originating from epithelial tissues, carcinomas.

The involvement of FGFR3 in such solid tumour development is linked to a constitutional activation : it may be activated by an autocrinal loop (ligand self-

production) and/or by activating mutations in *FGFR3*. Surprisingly, such mutations are found in primary tumours and are somatic mutations (genomic DNA mutations).

So far, the only *FGFR3* isoform which has been identified in epithelium is the *FGFR3*-IIIb isoform.

5 The invention thus relates to a method and kits for detecting such pathologies.

 According to another aspect, the invention also relates to drugs capable of treating such pathologies.

 According to still another aspect, it relates to transgenic animals enabling
10 the efficiency of such drugs to be tested as well as to cell lines transfected with the different forms of *FGFR3* (useful *in vitro* and *in vivo*).

 The method of the invention for detecting carcinomas in a biological sample comprises identifying *FGFR3* mutations.

 Standard methods can apply for such an identification such as
15 immunohistochemistry, or detection of the corresponding RNA, DNA, and encoded protein contained in said sample, particularly after extraction thereof. A common way for such a detection comprises amplifying by PCR, RT-PCR or RT-PCR SSCP (single strand conformation polymorphism) with *FGFR3* specific primers and revealing the amplification products according to the usual methods. A corresponding embodiment is
20 exemplified in the examples given hereinafter. Another common way comprises the use of antibodies and the detection of the antigen-antibody reaction with appropriate labelling.

 The activating function of a mutation can be determined by observation
of activating signals such as receptor phosphorylation, cell proliferation (e.g. thymidine
25 incorporation) or indirect effects such as calcium influx, phosphorylation of target sequences.

 More particularly, said identification comprises screening for single nucleotide mutation(s) in the genomic DNA and/or its products, i.e. RNA, protein, the term "product" also encompassing cDNA.

30 Particularly, said method comprises screening for mutations creating cysteine residues in the extracellular or transmembrane domains of the receptor.

 Alternatively, or in combination with the foregoing embodiment, it comprises screening for mutations resulting in at least one amino-acid substitution in the kinase domain of the receptor.

35 It particularly comprises screening of activating mutation(s) of *FGFR3*, notably such as above-described.

 More particularly, the method of the invention comprises screening for mutation(s) in exon 7, encoding the junction between immunoglobulin-like domains II

and III of FGFR3, in exon 10, encoding the transmembrane domain, in exon 15, encoding the tyrosine kinase domain I, and/or in the exon encoding the C-terminal part.

Advantageously, the method of the invention comprises screening for missense mutations such as implicated in thanatophoric dysplasia, NSC, achondroplasia, saddan, or hypochondroplasia.

Such FGFR3 mutations notably comprise R248C, S249C, G372C, S373C, Y375C, K652E, K652M, J809G, J809C, J809R, J809L, P250R, G377C, G382R, A393E, N542K (codons are numbered according to FGFR3-IIIb cDNA open reading frame).

The following FGFR3 mutations will be particularly identified : R248C, S249C, G372C, K652E and Y375C.

Said biological sample used in the method of the invention will advantageously comprise a tissue, bone marrow, or a fluid such as blood, urine, deriving from a warm-blooded animal, and more especially from a human.

Said method is particularly useful for detecting carcinomas, such as human bladder and cervix carcinomas. A major issue in superficial bladder cancer is to distinguish tumours which will progress from those which will not. Insights into the genetic and epigenetic alterations involved in bladder cancer is expected to provide useful information to facilitate this distinction. In that respect, the invention provides means to resolve the dilemma between a bladder-sparing strategy versus cystectomy and will contribute to a more individualised intravesical instillation and endoscopic monitoring policy.

Indeed, as shown by the results given in the examples, *FGFR3* appears to be a major oncogene in Ta, T1 bladder carcinomas. The *FGFR3* mutations appear to be frequently associated with tumours that do not progress. Multivariate analysis showed that *FGFR3* mutation status remained a statistically significant predictor of good outcome. *FGFR3* mutations thus provide clear-cut information, which may complement stage and grade. The use of these mutations alone and/or in combination with other predictors of tumour aggressiveness will then provide relevant prognostic information.

Said method, will also be used for detecting for example lung, breast, colon, skin cancers.

The method of detection according to the invention applies to the diagnostic of carcinomas, as well to the prognosis, or the follow-up of the efficiency of a therapy.

Said method will advantageously be performed by using kits comprising the appropriate reagents and a notice of use.

According to another aspect, the invention relates to drugs having an anti-proliferative effect on carcinoma cells. Such drugs comprise, as active principle(s)

agent(s) which act by inhibition of FGFR3 DNA synthesis or by inhibition of its expression products (RNA, proteins). Particularly, such drugs contain tyrosine kinase inhibitors specific for FGFR3.

Other appropriate inhibitors comprise antibodies directed against FGFR3, and particularly against at least one extracellular Ig-like domain thereof. Advantageously said antibodies are specific for FGFR3-IIIb. Preferred antibodies are monoclonal ones, and particularly antibodies modified so that they do not induce immunogenic reactions in a human body (e.g. humanized antibodies).

Other appropriate inhibitors comprise antisens oligonucleotides directed against a wild or mutated *FGFR3* isoform.

The administration and the posology of said inhibitors will be determined by the one skilled in the art depending on the carcinoma to be treated, the weight and age of the patient. For example, antibodies will be administered by the injectable route.

The invention thus gives means of great interest for detecting and treating carcinomas, taking into account the fact that cancers originating from epithelial tissues (carcinomas) represent approximately 90 % of malignant neoplasms.

The invention also relates to cell lines capable of expressing FGFR3 mutated forms. Particularly, the invention relates to FGFR3 S249C mutated forms. T24 cell lines constitutively expressing FGFR3 S249C mutated forms and HeLa cell lines expressing FGFR3 S249C mutated forms in an inducible manner have thus been obtained (for example see ref.(6)).

By injecting such cell lines to nude mice, an increased tumorigenicity was observed.

According to the invention, such cell lines are useful *in vitro* (follow up of the receptor phosphorylation) or *in vivo* (examination of the tumorigenicity of nude mice) to study the inhibitor effect against FGFR3.

Cell lines transfected with FGFR2, FGFR1 or FGFR4 are particularly useful for studying the specificity of inhibitors to be tested.

According to still another object, the invention relates to constructions capable of expressing by transgenesis a FGFR3 mutated form in epitheliums and the transgenic animals thus obtained which are characterized by the fact that they comprise such constructions.

Examples of constructions intended for injection in animal germinal cells comprise a keratin promoter, particularly keratin 14 promoter and cDNA of mutated FGFR3.

Other advantages and characteristics of the invention will be given in the following examples wherein it will be referred to

- figures 1A - 1B which give FGFR3-IIIb gene activating mutations in primary tumours,

- figures 2A - 2E which refer to FGFR3-IIIb wild (2A) and mutated pro-oncogenic (2B-2T) sequences. It will be noted that the sequences of figures 2B to 2T, as such, enter into the scope of the invention. There may be silent polymorphisms all along the sequence, so there may be in fact several possible sequences for each mutant, and

- figures 3a and 3b which respectively represent a) Kaplan-Meier progression-free survival curves according to *FGFR3* mutations (dotted line: mutated *FGFR3*, solid line: non-mutated *FGFR3*; log rank test $p=0.014$) ; b) Kaplan-Meier disease-specific survival curves according to *FGFR3* mutations (dotted line: mutated *FGFR3*, solid line: non-mutated *FGFR3*; log rank test $p=0.007$)

Example 1 : *FGFR3* gene mutations in bladder and cervix carcinomas

FGFR3-IIIb and *FGFR3-IIIc* transcript levels were examined by reverse transcription-polymerase chain reaction (RT-PCR) in 76 primary bladder carcinomas and 29 primary invasive cervical carcinomas.

FGFR3-IIIb, the sole isoform to be significantly expressed, was detected in 72 out of 76 (94%) bladder carcinomas and 27 out of 29 (93%) cervical carcinomas.

A PCR-SSCP analysis was then conducted on both reverse transcribed RNA and genomic DNA to screen for *FGFR3* coding sequence variants in 26 bladder and 12 cervix cancers expressing the gene. The results are illustrated in figures 1a and 1b which gives the identification of *FGFR3* gene mutations in human carcinomas :

- a: gives the identification of somatic mutations by direct sequencing of PCR products. Normal constitutional DNA ; Tumour, tumour DNA.

- b: gives *FGFR3* mutations associated with skeletal disorders and cancers.

The schematic structure of *FGFR3* is depicted (Ig I-III, immunoglobulin like domains ; TM, transmembrane domain ; TK-1 and -2, tyrosine kinase domains) and the locations of the known human missense mutations associated with thanatophoric dysplasia (TD) and severe achondroplasia (SADDAN), bladder and cervix carcinomas (carc.) and multiple myeloma (MM) are indicated. Usual amino acid abbreviations are used to point out the mutation found in each pathological situation. The mutations at codon 807 incriminated in TD replaces a Stop codon (J) by an amino acid (G, C, R or L) and the mRNA thus continues to be translated until another in-frame Stop codon is reached 423 nucleotides downstream thus leading to a 141 amino acid longer protein.

Abnormally migrating bands were observed for certain samples (Fig. 1a) and direct sequencing of PCR products revealed single nucleotide substitutions in 9 out of 26 bladder carcinomas (35 %) and 3 out of 12 (25 %) cervix carcinomas (Fig. 1b and table 1).

Table 1

Summary of FGFR3 gene mutations in primary bladder and cervix cancers					
Sample	Histopathol.	Codon	Nt Position	Mutation	Predicted effect
1447, bladder	carc., Ta G2	249	746	TCC to TGC	Ser to Cys
342, bladder	carc., T1a G1	249	746	TCC to TGC	Ser to Cys
813, bladder	carc., T1a G1	372	1114	GGC to TGC	Gly to Cys
1393.1, bladder	carc., T1a G3	249	746	TCC to TGC	Ser to Cys
506, bladder	carc., T1b G2	372	1114	GGC to TGC	Gly to Cys
1084, bladder	carc., T1b G3	652	1954	AAG to GAG	Lys to Glu
745.1, bladder	carc., T2 G3	248	742	CGC to TGC	Arg to Cys
1077, bladder	carc., T3 G2	249	746	TCC to TGC	Ser to Cys
1210, bladder	carc., T3 G2	249	746	TCC to TGC	Ser to Cys
4.13, cervix	carc., stage II	249	746	TCC to TGC	Ser to Cys
4.139, cervix	carc., stage II	249	746	TCC to TGC	Ser to Cys
6.96.1, cervix	carc., stage II	249	746	TCC to TGC	Ser to Cys

Histopathol., histopathological classification of the tumours (carc., carcinoma : TNM and HUGO classifications are used respectively for bladder and cervix cancers) ; codon and mutated nucleotide (Nt position) are numbered according to FGFR3-IIIb cDNA open reading frame.

Mutations were found in the following exons

- exon 7, encoding the junction between immunoglobulin-like domains II and III of FGFR3 (one C-to-T transition at codon 248 in patient 745.1 and a C-to-G substitution at codon 249 in patient 1447) ;

- exon 10, encoding the transmembrane domain (a G-to-T-transversion at codon 372 in patient 813)

- exon 15, encoding the tyrosine kinase domain II (a A-to-G transition at codon 652 in patient 1084).

Analysis of matched constitutional DNA from the patients for which such material was available (n=8) demonstrated the somatic nature of these *FGFR3* mutations (Figure 1).

Strikingly, each of the FGFR3 missense mutations identified herein, i.e. R248C, S249C, G372C and K652E, are implicated in thanatophoric dysplasia (TD).

Given the presence of two additional amino-acids in the IIIb isoform expressed in epithelial cancers as compared to the IIIc isoform expressed in bone, the G372C and K652E mutations are indeed equivalent to the G370C and K650E mutations responsible for TD.

5 The S249C mutation was the most commonly observed, affecting 5 out of 9 (55 %) bladder cancers and all of the cervical cancers (3 out of 3, 100 %) in which *FGFR3* gene alterations have been identified so far.

 The R248C, S249C and G372/370C mutations create cysteine residues in the extracellular or transmembrane domains of the receptor and the K652/650E mutations results in amino-acid substitution in the kinase domain of the receptor.

Example 2 : Inhibitors

 A way to test the different *FGFR3* inhibitors comprises transfecting cell lines so that they express the mutated forms of *FGFR3*, or wild type *FGFR3* or just the neomycin or hygromycin resistant gene under the control of a strong promoter, such as CMV, RSV, SV40 promoters. The tumorigenic properties of these cell lines can then be compared *in vitro* or *in vivo* in nude mice. The different inhibitors will be tested *in vitro* or *in vivo* using these different cell lines. Phosphorylation, proliferation or indirect effects of *FGFR3* such as calcium influx will be measured. Transgenic mice expressing in various epithelia the mutated *FGFR3* can thus be derived thereof. Those mice developing tumours are useful tools for testing the efficiency of candidate inhibiting drugs. Such transgenic animals fall also into the scope of the present invention.

Example 3 : *FGFR3* mutations in Ta, T1 tumours in bladder cancer.

 Bladder cancer is a disease with a spectrum of forms and is highly unpredictable. At the time of initial diagnosis, approximately 80% of patients present with a superficial tumour. Superficial bladder cancers include carcinoma *in situ* (Tis), Ta and T1 lesions (TNM classification). Ta/T1 lesions are mostly papillary urothelial carcinomas: Ta lesions do not invade the basement membrane, whereas T1 lesions invade the lamina propria, but do not invade the detrusor muscle of the bladder wall. Carcinoma *in situ* are flat, cytologically high-grade carcinomas, confined to the urothelium. Primary isolated carcinoma *in situ* is a very rare entity and is more commonly associated with Ta/T1 lesions. Despite transurethral resection alone or combined with adjuvant intravesical therapies, more than one half of patients with Ta/T1 tumours suffer recurrences. In most cases, recurrences are also superficial, but about 5% of Ta and 30-50% of T1 tumours progress in an unpredictable manner to muscle invasion with a high risk of development of metastases and death from bladder cancer.

 The management of superficial bladder cancer is based on clinicopathological parameters. Three groups of tumours can be defined. of low,

intermediate and high risk, according to their potential for recurrence and progression. This classification is used to recommend adjuvant intravesical therapies and bladder monitoring, but it is not a sufficiently sensitive discriminant for use in determining the appropriate treatment and mode of surveillance for a given patient. Although Bacille Calmette-Guérin (BCG) therapy appeared to be the most effective regimen for the high-risk group, long-term results indicate that progression occurs in 40% by 10 years and in more than 50% by 15 years. For some researchers, these findings justified the use of up-front radical cystectomy in high-risk superficial urothelial carcinomas, despite the risk of overtreating a significant number of patients. Follow-up of Ta and T1 superficial bladder cancers constitutes most of the workload of urologists involved in the management of bladder cancer. The current strategy is based on frequent cystoscopic evaluations using a schedule that is largely empirical, without considering the individual characteristics of the tumour.

The limitations of the current management of bladder cancer demonstrate the need for prognostic markers, making possible the use of selective aggressive treatments for patients at high risk of progression while sparing low-risk patients from unnecessary procedures. A number of chromosomal loci and specific genes have been implicated in bladder tumorigenesis. Losses of all or part of chromosome 9 in many TaG1 tumours suggests that the inactivation of a gene or genes on chromosome 9 may be an early event in urothelial transformation. The prognostic significance of losses on chromosome 9 is unclear. Alterations of the *P53* and *RB* genes controlling the G1 cell cycle checkpoint have been clearly delineated and are associated with the aggressiveness of superficial and invasive bladder cancers. Despite these recent insights into the molecular mechanisms of bladder carcinoma progression, these markers have not yet had any impact on clinical practice.

The following assays have been performed to assess the reliability, as markers, of the FGFR3 mutations.

Material and method

30 Patients and tissue samples

Seventy four specimens of superficial Ta, T1 bladder carcinomas were obtained from 74 patients by transurethral resection performed at the Henri Mondor hospital, Créteil, France, from January 1988 to December 1998. Tumours were staged according to the TNM classification (1) and graded according to criteria recommended by the World Health Organisation (2). This series consisted of 25 pTa and 49 pT1 tumours, with 28 grade G1, 33 grade G2 and 13 grade G3 tumours. The 64 men and 10 women had a mean age of 64 years (range: 29 to 94 years). None of the patients had any detectable distant metastases at the time of transurethral resection. Patients were treated

by transurethral resection (TUR) alone (n=25), TUR followed by mitomycin C instillation (n=10) or TUR and BCG (n=39) according to the French Committee for Urologic Oncology (CCAFU) recommendations. There was no change in the policy for treating superficial bladder cancer during the study period. Progression was defined as the occurrence of a pT2 or higher stage or appearance of lymph node invasion or metastasis or death from cancer. Disease-specific survival curves were plotted using death from urothelial cancer as the endpoint. Follow-up was based on systematic cystoscopy and cytology, and imaging studies only when indicated. All outpatient visits and hospital admissions were recorded in a database from which the study data were calculated.

Tumour DNA was extracted from formalin-fixed and paraffin-embedded tissue or samples freshly frozen in liquid nitrogen (4). Normal DNA samples from peripheral blood were available for 27 patients.

15 *FGFR3* mutation analysis

Mutations in the *FGFR3* gene were detected by SSCP analysis. Exons 7, 10, 15 and 20 of the *FGFR3* gene were analysed because these exons harbour all the mutations previously identified in bladder carcinomas and thanatophoric dysplasia. All mutations detected by SSCP analysis were confirmed by direct bidirectional sequencing of tumour genomic DNA. Matched normal DNA, if available, was sequenced on both strands to demonstrate the somatic nature of these mutations.

Statistical methods

Associations between *FGFR3* mutation status and other data (sex, age, stage and grade) were tested using χ^2 and Student's t tests. Progression-free and disease-specific survival curves were plotted using Kaplan-Meier estimates. Survival distributions were compared using the log-rank test. Cox's proportional hazards regression model was used to test the effect of mutations, while simultaneously accounting for baseline patient and tumour characteristics. The influence of the covariates on the *FGFR3* mutation effect was assessed in multivariate analysis involving a forward stepwise procedure and a backward stepwise procedure, using the MPRL (maximum partial likelihood ratio) method. The limit to enter a term was 0.15 and the limit to remove a term was 0.10. Statistical analyses were performed using BMDP® and S-Plus® software.

Results

FGFR3 missense mutations were observed in 41 of the 74 (55%) Ta, T1 bladder tumours. The *FGFR3* mutations found are described in Table 2 below :

Table 2

Number of tumours (%)	Codon*	nt position*	Mutation	Predicted effect
5 (12%)	248	742	CGC -> TGC	Arg -> Cys
28 (68.5%)	249	746	TCC -> TGC	Ser -> Cys
5 (12%)	372	1,114	GGC -> TGC	Gly -> Cys
2 (5%)	375	1,124	TAT -> TGT	Tyr -> Cys
1 (2.5%)	652	1,954	AAG -> GAG	Lys -> Glu

* codon and mutated nucleotide (nt position) are numbered according to FGFR3-IIIb cDNA open reading frame. FGFR3-IIIb is the isoform expressed in epithelial cells.

5

S249C was the commonest mutation and was found in 16 of the 21 (76%) mutated Ta tumours and 12 of the 20 (60%) mutated T1 tumours. Matched constitutional DNA, available in 15 of the cases of tumour with mutations, contained wild-type sequences, demonstrating the somatic nature of these mutations.

10

The correlation between sex, age, stage, grade and *FGFR3* mutation status is given Table 3 :

Table 3

	<i>FGFR3</i> wild type	<i>FGFR3</i> mutant	p value (χ^2 or Student's t test)
Sex			
Male	29	35	
Female	4	6	0.9779
Age (years)			
mean	64.30	63.22	
range	[29.15-86.10]	[34.3-94.4]	0.7393
Stage			
Ta	4	21	
T1	29	20	0.001
Grade			
G1	7	21	
G2	14	19	
G3	12	1	0.0003

Statistically significant correlations were observed between *FGFR3* mutations and low stage (p=0.001) and low grade (p=0.0003), but not between these mutations and age or sex (Table 2).

With a median follow-up of 4.3 years (range: 6 months to 11 years), 3 patients progressed and one died in the mutated tumour group (n=41 patients) whereas ten patients progressed and eight died in the non-mutated tumour group (n=33 patients).

The median follow-up was 5.6 years (range: 7 months to 11 years) in the non-mutated group and 4.1 years (range: 6 months to 9 years) in the mutated group.

To examine *FGFR3* mutations as a marker of patient outcome, we calculated Kaplan-Meier progression-free survival and disease-specific survival probability curves for the two groups of patients and examined the differences using the log rank test. Progression-free and disease-specific survival indicated that *FGFR3* mutations were associated with a lower risk of progression ($p=0.014$) and longer survival ($p=0.007$) (Figure 3). We tested several variables (age, sex, stage, grade) but only stage was significantly associated with progression and survival in univariate analysis. If only T1 patients were analysed, the correlation was still significant for disease-specific survival ($p=0.03$) and close to significance for progression-free survival ($p=0.052$).

Multivariate analysis was used to determine whether the correlation between *FGFR3* mutation status and progression-free survival or disease-specific survival was independent of other outcome predictors. For progression-free survival, the following covariates were introduced into the Cox model: mutation, stage, grade and sex. For disease-specific survival, mutation and grade were the only covariates introduced into the model, as no disease-related deaths were observed among female or Ta patients. If *FGFR3* status was entered into the model, neither stage nor grade provided any additional prognostic value for tumour progression. In the analysis of disease-specific survival, *FGFR3* mutation was also the only covariate to be entered into the model, as grade did not provide any additional prognostic information. Relative risks and their 95% confidence intervals (CI) are shown in Table 4.

25

Table 4

	Progression		Disease-specific Survival	
	Relative Risk	95% CI	Relative Risk	95% CI
<i>FGFR3</i>				
Wild-type	1		1	
Mutant	0.23	(0.06; 0.83)	0.10	(0.01; 0.80)
Other variables do not significantly contribute to the model				

Forward and backward procedures both yielded the same model.

As shown by the above results, the FGFR3 activating mutations were frequent in bladder carcinomas.

All the carcinomas having a mutated receptor expressed said receptor at levels similar or above those observed with normal tissues. Immunohistochemical methods will then advantageously be used for revealing the receptor.

FGFR3 mutation detection in bladder carcinomas appears to be a good pronostic, giving then to the clinicians valuable means for treating and observing carcinomas, which represent a medical problem due to the high frequency of recurrences.

By using SSCP or PCR coupled to an enzymatic restriction S249C mutation specific (which represent 75% of the mutations) on patients having bladder carcinomas with S249C mutation, the mutation could be detected in urine in 60% of the cases.

Example 4: Detection of FGFR3 mutations in patients' urines

Genomic DNA is extracted from patients' urines and amplified by PCR, in the presence of ³²P- labelled dCTP, using standard methods. The following primers were used for detecting S249C mutation :

5'-CAG CAC CGC CGT CTG GTT GG-3' and 5'-AGT GGC GGT GGT GGT GAG GGA G-3'.

30 cycles of PCR are performed.

The amplification products are digested by *Cac8I*. An additional site is created by *FGFR3* mutation and a corresponding band is observed on an electrophoretic gel.

Similarly the following primers and enzymes can be used to detect :

R248C mutation :

Primers : 5'-TGT GCG TCA CTG TAC ACC TTG CAG-3' and 5'-AGT GGC GGT GGT GGT GAG GGA G-3'

Enzyme : *Bsi* HKA I

K652E mutation :

Primers : 5'-TGG TGA CCG AGG ACA ACG TGA TG-3' and 5'-AGG GTG TGG GAA GGC GGT GTT G-3'

Enzyme : *Bsm* A I

G372C mutation :

Primers : 5'-CCT CAA CGC CCA TGT CTT TTC AGC-3' and 5'-CTT GAG CGG GAA GCG GGA GAT CTT G-3'

Enzyme : *Pst* I

Y375C mutation :

Primers : 5'-CCT CAA CGC CCA TGT CTT TTC AGC-3' and 5'-CTT GAG CGG
GAA GCG GGA GAT CTT G-3'

5 Enzyme : *Bsg* I

References

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CLAIMS

1/ A method for detecting carcinomas in a biological sample, comprising
5 identifying FGFR3 mutations.

2/ The method of claim 1, comprising screening for single nucleotide
mutation(s) in nucleic acids of the group comprising genomic DNA, RNA or cDNA.

10 3/ The method of claim 1, comprising screening for single mutation(s) in
proteins.

4/ The method of claim 1, comprising screening for mutations creating cysteine
residues in the extracellular or transmembrane domains of the receptor.

15 5/ The method of claim 1, comprising screening for mutations resulting in at
least one amino-acid substitution in the kinase domain of the receptor.

20 6/ The method of claim 5, comprising screening of activating mutation(s) of
FGFR3.

7/ The method of claim 6, comprising screening of activating mutation(s) of
FGFR3-IIIb.

25 8/ The method of claim 1, comprising screening for mutation(s) in the group
comprising exon 7, encoding the junction between immunoglobulin-like domains II and
III of FGFR3, exon 10, encoding the transmembrane domain, exon 15, encoding the
tyrosine kinase domain I, and the exon encoding the C-terminal part.

30 9/ The method of claim 1, comprising screening for missense mutations such as
implicated in thanatophoric dysplasia, NSC, achondroplasia, SADDAN, or
hypochondroplasia.

35 10/ The method of claim 9, wherein the mutations comprise R248C, S249C,
G372C, S373C, Y375C, K652E, K652M, J809G, J809C, J809R, J809L, P250R,
G377C, G382R, A393E, N542K.

11/ The method of claim 9, comprising screening R248C, S249C, G372C, K652E and Y375C mutations.

12/ The method of claim 1, wherein the biological sample is selected in the group comprising a tissue, bone marrow, or a body fluid.

13/ The method of claim 12, wherein said body fluid is selected in the group comprising blood, urine from a warm-blooded animal.

14/ The method of claim 13, wherein said body fluid is from a human.

15/ The method of claim 1 for detecting human bladder and cervix carcinomas.

16/ The method of claim 1, for detecting lung, breast, colon, skin cancers.

17/ The pharmaceutical preparations having an anti-proliferative effect on carcinoma cells comprising an effective amount of agent(s) which act by inhibition of FGFR3 DNA synthesis or by inhibition of its expression products.

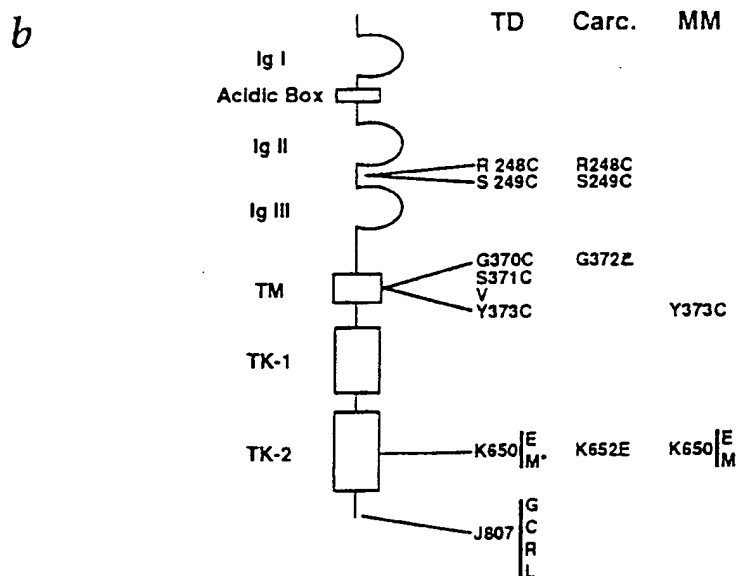
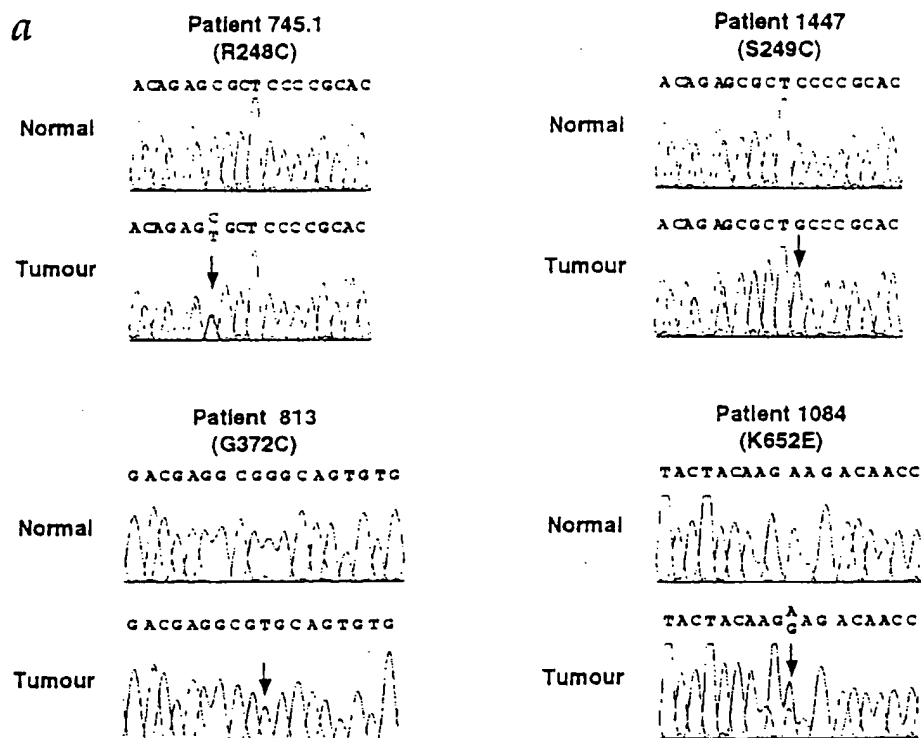
18/ The pharmaceutical preparations of claim 17, comprising tyrosine kinase inhibitors specific for FGFR3.

19/ The pharmaceutical preparation of claim 18, comprising antibodies directed againstp FGFR3.

20/ The pharmaceutical preparations of claim 17, comprising antisens oligonucleotides directed against a wild type or mutated FGFR3 isoform.

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FIGURE 1



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Figure 2A

Wild Type FGFR3-IIIb:

ATGGGCGCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCTCGTGGGGCGAGCGGCAGAAGTCCCCGGGCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCACAGGAGTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACCGGCAGGGAGTTCGCGGGCGAGCACCAGTGGAGGATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGGCTCGGACCGCGGCACTACACCTGCGTCTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGCCATCCTGCAGGCGGGGCTGCCGGCCAACAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCTGCAAGGTGTACAGTACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCCGACGGCACACCCTACGTTACCGTGCTCAAGTCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCTGGCCAATGTGTGCGAGCGGGACGGGGCGAGTACCTCTGTGAGCCACCAATTTATAGGCGTGGC
CGAGAAGGCCCTTTTGGCTGAGCGTTCAGGGGCCCGAGCAGCCGAGGAGGAGTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCTGTTTATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCTG
CGCAGCCCCCAAGAAAGGCCTGGGCTCCCCCACCCTGCACAAGATCTCCGCTTCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCTCCATGAGCTCCAACACACCCTGGTGCGCATCGCAAGGCTGTCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGTGCCTGCCGACCCCAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCCT
GGGGAGGGCTGCTTCGGCCAGGTGGTTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTGCGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGGCGCTGCACGCAGGGCGGGCCCCCTGTACGTGCTGGTGGAGTACGGC
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGGCCCCCGGGCTGGACTACTCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCTGTGCTTACCAGGTGGCCCGGGCATGGAGTACTTGGCCTCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCCGAATGTGTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCCGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCTGAGGC
CTTGTGTGACCGAGTCTACACTCACCAGAGTGACGTCTGTGCTTGGGGTCTGCTCTGGGAGATCTTACGCTGGGGG
GCTCCCCGTACCCGGCATCCCTGTGGAGGAGCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCCGCCAAC
TGACACACGACCTGTACATGATCATGCGGGAGTGTGGCATGCCGCGCCCTCCAGAGGCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCTTACCCTGACGTCCACCGACGAGTACCTGGACCTGTGGCGCCTTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTGCCACGACCTGTGCCCCGGGCCCA
CCCAGCAGTGGGGCTCGCGGACGTGA

Figure 2B

Mutant R248C FGFR3-IIIb:

ATGGGCGCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCTGTGGGCGAGCGGCAGAAGTCCCGGGCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCGCGCGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCACAGGAGACTCCGGGGCCTA
CAGCTGCCGCGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGGCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCAACACCGTCCGCTTCCGCTGCCCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCTCGGACCGCGGCAACTACACCTGCGTCTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGTGGAGTGTCCCCGACCGGCCATCCTGCAGGCGGGGCTGCCGGCCAACAGACGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCCGACGGCACACCTACGTTACCGTGTCAAGTCTTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCTGGCCAATGTGTGAGCGGGGACGGGGCGAGTACCTCTGTGAGCCACCAATTTATAGGCGTGGC
CGAGAAGGCCCTTTTGGCTGAGCGTTACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGACGCGATCCTCAGCTACGGGGTGGGCTTCTTCTGTTCATCCTGGTGGTGGCGCTGTGACGCTCTGCCGCTC
CGCAGCCCCCCCCAAGAAAGGCTGGGCTCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCAGCATCGCAAGGCTGTCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCCGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAACATCATCAACCTGCTGGGCGCTGCACGCAGGGCGGGCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGGCCCCGGGGCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCTGTGCTTACCAGGTGGCCCGGGGATGGAGTACTTGGCCTCCAGAG
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCCGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTGTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCTTTGGGGTCTGCTCTGGGAGATCTTACGCTGGGGG
GCTCCCCGTACCCCGCATCCCTGTGGAGGAGCTTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGTGGCATGCCGCGCCCTCCAGAGGCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCAAGCTCCAGCTCCTCAGGGGACGACTCGGTGTTTGGCCACGACCTGCTGCCCCGGCCCCA
CCAGCAGTGGGGGCTCGCGGACGTGA

Figure 2c

Mutant S249C FGFR3-IIIb:

ATGGGCGCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCTCGTGGGCGGAGCGGCAGAACTCCCGGGCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCGCCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGGCCCTCGGAGCGTGTCTGGTGGGGCCCCAGCGGTGCAGGTGCTGAATGCCTCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGTACGCGAGCGCTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCTTACTGGACACGGCCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCGGGCCGCCAACCCGTCCGCTTCCGCTGCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAAGCGCAGGGAGTTCCGCGGGCAGCACCCGATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGGCTCGGACCGCGGCAACTACACCTGCGTCTGGAGAACAAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTGCCCGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCCGACGGCACACCTTACGTTACCGTGCTCAAGTCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCTCCGCTGGCCAATGTGTGCGAGCGGGACGGGGCGAGTACCTCTGTGAGCCACCAATTTATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTACCGGGCCCCGAGCAGCCGAGGAGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCTGTTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCTG
CGCAGCCCCCAAGAAAGGCCTGGGCTCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCATCGCAAGGCTGTCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCAATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCTGCACGAGGGCGGGCCCCCTGTACGTGCTGGTGGAGTACGG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGGGCGGCCCGGGCCTGGACTACTCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCTGTGCTTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCCGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTGTGACCGAGTCTACACTACCCAGAGTGACGTCTGGTCTTTGGGGTCTGCTCTGGGAGATCTTACGCTGGGGG
GCTCCCCGTACCCGGCATCCCTGTGGAGGAGCTCTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGTGGCATGCCGCGCCCTCCAGAGGGCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTGCGCGCCTTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGGCCACGACCTGCTGCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGTGA

Figure 2D

Mutant G372C FGFR3-IIIb:

ATGGGGCCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTSGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAGTCCCGGGGCCAGAGCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCGGGGGTGGTCCCATGGGGCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCTCGGAGCGTGTCTGGTGGGGCCCCAGCSGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGGCCCTTACTGGACAGGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCAGCCSCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAGCGTGGTGCCCTCGGACCGCGGCACTACACCTGCGTGGTGGAGAACAAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGAGCTGTGGAGCGTCCCCGACCGGGCCCATCCTGCAGGCGGGGCTGCCGGCCAAACAGACGGCGGTGCT
GGGCAGCGAGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGGCCGGACGGCACACCTACGTTACCGTGTCAAGTCTTGATCAGTGAGAGTGTGGAGGCGGAC
GTGCGCTCCGCTGGCCAATGTGTGCGAGCGGGACGGGGCGAGTACCTCTGTGAGCCACCAATTTATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGTGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCTG
CGCAGCCCCCAAGAAAGGCCTGGGCTCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGGCATCGCAAGGCTGTCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCAACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTGCGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGGCGCCCCCGGGCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCTGTGCTACCAAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
AGTGCATCCACAGGACCTGGCTGCCCCGAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTGTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCTTTGGGGTCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGTGGCATGCCGCGCCCTCCCAGAGGGCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCTTACCCTGACGTCCACCGACGAGTACCTGGACCTGTGCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCAAGCTCCAGTCTCAGGGGACGACTCCGTGTTGCCACGACCTGCTGCCCCCGGGCCCA
CCCAGCAGTGGGGGCTCGCGGACGTGA

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Figure 2E

Mutant K652E FGFR3-IIIb:

ATGGGCGCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCTGTTGGGCGAGCGGCAGAAAGTCCCGGGCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCGCCCCGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCTGTGGGGCCCGAGCGGTGCAGGTGCTGAATGCCTCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCGCTGCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCGCGGGCGAGCACCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAGCGTGGTGCCTCGGACCGCGGCAACTACACCTGCGTCTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGACCGGCCATCCTGCAGCGGGGCTGCCGGCCAACAGACGGCGGTGCT
GGCAGCGACGTGGAGTTCACCTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCAGGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCGGACGGCACACCTACGTTACCGTGTCAAGTCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCCTGGCCAATGTGTGCGAGCGGGACGGGGCGAGTACCTCTGTGAGCCACCAATTTATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCTGTTTATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCTG
CGCAGCCCCCAAGAAAGGCTGGGCTCCCCCACCCTGCACAAGATCTCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGGCATCGCAAGGCTGTCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAATGGGAGCTGTCTCGGGCCCGGCTGACCTGGGCAAGCCCCCT
GGGAGGGCTGCTTCGGCCAGGTGGTGTGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCAAGCCTGTACCCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTGCGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGCCCCCGGGCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCTGTGCTACAGGTGGCCCGGGGATGGAGTACTTGGCCTCCAGAG
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCCGGACGTGCACAACCTCGACTACTACAAGGAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCTGAGGC
CTTGTGTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCTTTGGGGTCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGACACACGACCTGTACATGATCATGCGGGAGTGTGGCATGCCGCGCCCTCCAGAGGGCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTGCGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCGAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGCCACGACCTGCTGCCCGGGCCCCA
CCAGCAGTGGGGGCTCGCGGACGTGA

Figure 2F

Mutant S373C FGFR3-IIb:

ATGGGCGCCCTGCCTGCGCCCTCGCGCTCTGCGTGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCTGTTGGGCGAGCGGCAGAAGTCCCAGGCGCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCACAGGAGACTCCGGGGCCTA
CAGTGGCGGCGAGCGGCTCAGCGAGCGGTAAGTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCGGGCGCCAAACACCGTCCGCTTCCGCTGCCAGCGGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCGGCGGGCAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCTGTGGAGAACAAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGGCCGGACGGCACACCTACGTTACCGTGTCAAGTCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCTGGCCAATGTGTGCGAGCGGGACGGGGCGAGTACCTCTGTGAGGCCACCAATTTTATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTACCGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCTGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCTGTTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCTG
CGCAGCCCCCAAGAAAGGCTGGGCTCCCCACCGTGACAAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCATCGCAAGGCTGTCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCCTT
GGGGAGGGCTGTCTCGGCCAGGTGGTTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCAAGCCTGTACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTGCGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGGCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGCCCCCGGGCCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCTGTGCTACAGGTGGCCCGGGGCGATGGAGTACTTGGCCTCCAGAG
AGTGATCCACAGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTGTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCTTTGGGGTCTGCTCTGGGAGATCTTACGCTGGGG
GCTCCCCGTACCCCGGCATCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGTGGCATGCCGCGCCCTCCAGAGGCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTGCGCGCCTTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCAAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGGCCACGACCTGCTGCCCCGGCCCCA
CCAGCAGTGGGGGCTCGCGGACGTGA

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Figure 2G

Mutant Y375C FGFR3-IIb:

ATGGGCGCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCSTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCTGTTGGGCGAGCGGCAGAAGTCCCCGGCCCGAGGCCCCAGCAGGAGCAGTGTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCTTACTGGACACGGCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATTTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCTCGGACCGCGGCAACTACACCTGCGTCTGGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGCCCATCTGCAGGCGGGGCTGCCGGCCAACAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCCGACGGCACACCTACGTTACCGTGTCAAGTCTCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCTCCGCTGGCCAATGTGTGCGGACGGGACGGGGCGAGTACCTCTGTGAGCCACCAATTTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTGTGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCTG
CGCAGCCCCCAAGAAAGGCCTGGGCTCCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCAGCATCGCAAGGCTGTCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAATGGGAGCTGTCTCGGGCCCCGGCTGACCTTGGGCAAGCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCCAAGCCTGTACCCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCTGCACGCAGGGCGGGCCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCGGGCTGGACTACTCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCTGTGCTACCAGGTGGCCCCGGGCATGGAGTACTTGGCCTCCCAGA
AGTGATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCCGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTGTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCTTTGGGGTCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGACACACGACCTGTACATGATCATGCGGGAGTGTGGCATGCCGCGCCTCCAGAGGGCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTGCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGCCAGGACACCCCAAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGGCCACGACCTGCTGCCCCGGCCCCA
CCAGCAGTGGGGCTCGCGGACGTGA

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Figure 2H

Mutant K652M FGFR3-IIb:

ATGGGCGCCCTGCGCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCCTGGGGAC
GGAGCAGCGCGTCTGTTGGGCGAGCGGCAGAAAGTCCCGGGCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCGCGCGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGGCCTCGGAGCGTGTCTGGTGGGGCCCCAGCGGTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGGCCCTTACTGGACACGGCCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCGGGCCGCAACACCGTCCGCTTCGCTGCCAGCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGGCAGCACCGCATTTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGGCCTCGGACCGCGGCAACTACACCTGCGTCTGGAGAACAAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGACCGGCCATCCTGCAGGCGGGGCTGCCGGCCAACAGACGGCGGTGCT
GGGCAGCGCAGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCCGACGGCACACCTACGTTACCGTGTCTCAAGTCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCTCGCAATGTGTGCGAGCGGGACGGGGCGAGTACCTCTGTGAGCCACCAATTTATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCTG
CGCAGCCCCCAAGAAAGGCCTGGGCTCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGGCATCGCAAGGCTGTCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAATGGGAGCTGTCTCGGGCCCGGCTGACCTGGGCAAGCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCAAGCCTGTACCGT
AGCCSTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTGCGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGGGCGGGCCCCCGGGCCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCTGTGCTACAGGTGGCCCGGGGCGATGGAGTACTTGGCCTCCAGCA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGTGTTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCCGGACGTGCACAACCTCGACTACTACAAGATGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTGTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCTTTGGGGTCTGCTCTGGGAGATCTTACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGTGGCATGCCGCGCCCTCCAGAGGGCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTGCGGCGCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCAAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTGCCACGACCTGCTGCCCCGGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGTGA

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Figure 2I

Mutant X809C FGFR3-IIIb:

ATGGGCGCCCTGCCTGCCCTCGCGCTCTGCGTGGCCGTGGCCATCSTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCTGTTGGGCGAGCGGCAGAAAGTCCCGGGCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCGCCCCGGGGTGGTCCCATGGGGCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCTTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCACAGGAGTCCCGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCTTACTGGACACGGCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCCGGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCTTCGGACCGCGGCACTACACCTGCGTCTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACAGACGGCGGTGCT
GGGCAGCGACGTGGAGTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCGGACGGCACACCTACGTTACCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCCTGGCCAATGTGTGCGAGCGGGACGGGGCGAGTACCTCTGTGAGGCCACCAATTTATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGTGGGCTTCTTCTGTTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTG
CGCAGCCCCCAAGAAAGGCCTGGGCTCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACCACTGGTGCGCATCGCAAGGCTGTCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTGAGCTGCCTGCCGACCCCAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTACCCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTGCGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGCCCCGGGCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCTGTGCTACCAAGTGGCCCGGGGCATGGAGTACTTGGCCTCCGAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCCGGGACGTGCACAACTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCTGAGGC
CTTGTGTGACCGAGTCTACACTCACCAGAGTGACGTCTGCTCTTGGGGTCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCTCCAGAGGGCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTGCGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCACTCCAGCTCCTCAGGGGACGACTCCGTGTTTGGCCACGACCTGCTGCCCCGGCCCCA
CCAGCAGTGGGGGCTCGCGGACGTGC

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Figure 2J Mutant 1

Mutant X809G FGFR3-IIIb:

ATGGGCGCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCTGTGGGGCGAGCGGCAGAAAGTCCCGGGCCAGAGCCCGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCGCCCCGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCTTACTGGACACGGCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACCCGTCCGCTTCCGCTGCCAGCCGCTGGCAACCCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGTGGAGCGCTCCCGCACCGGCCATCCTGCAGGCGGGGCTGCCGGCCAAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCCGACGGCACACCCTACGTTACCGTGCTCAAGTCTTGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCTGGCCAATGTGTGCGAGCGGGACGGGGCGAGTACCTCTGTGAGCCACCAATTTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCGAGCAGCCGAGGAGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGTGGGCTTCTTCTGTTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCTG
CGCAGCCCCCAAGAAAGGCCTGGGCTCCCCACCGTGACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCCT
GGGGAGGGCTGCTTCGGCCAGGTGGTTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTCACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTGCGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGCCCGGGCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCTGTGCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCAGAG
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTGTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCTTTGGGGTCTGCTCTGGGAGATCTTACGCTGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCAGAGGGCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTGCGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCAAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGGCCACGACCTGCTGCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGGGA

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Figure 2K Mutant 2

Mutant: X809G FGFR3-IIIb:

ATGGGCGCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCTGTTGGGCGAGCGGCAGAAAGTCCCGGGCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCGCCCCGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCTTCGGAGCGTGTCTGTTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCACAGGAGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCTTACTGGACACGGCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATTTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGGCTCGGACCGCGGCACTACACCTGCGCTCGTGGAGAACAAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCCGACGGCACACCCCTACGTTACCGTGCTCAAGTCTTGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCTGGCCAATGTGTGGAGCGGGACGGGGGCGAGTACCTCTGTGAGCCACCAATTTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCTGTTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCTG
CGCAGCCCCCAAGAAAGGCCTGGGCTCCCCACCGTGACAAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCAAGCCTGTACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTGCGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGGCCCCCGGGCTGGACTACTCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCTGTGCTACCAGGTGGCCCGGGGCGATGGAGTACTTGGCCTCCAGAG
AGTGCAATCCACAGGGACCTGGCTGCCCCGAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTGTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCTTTGGGGTCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCAGAGGCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTGCGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCAAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGGCCACGACCTGCTGCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGAGA

Figure 2L Mutant 3

Mutant X809G FGFR3-IIIB:

ATGGGCGCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCTCGTGGGGCGAGCGGCAGAAAGTCCCGGGCCAGAGCCCGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGGCCCTCGGAGCGTGTCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCACGAGGACTCCGGGGCCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGGCCCTTACTGGACACGGCCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCACGCCGTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAAGCGCAGGGAGTTCCGCGCGCAGCACCAGCATTTGAGGCGATCAAGCTGCCGCATCAGCAGTGGAGCCTGG
TCATGGAAGCGTGGTGGCCCTCGGACCGCGGCAACTACACCTGCGTCTGGAGAACAAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCGCACCAGGCCCATCTGCAGGCGGGGCTGCCGGCCAACAGACGGCGGTGCT
GGGCAGCGCAGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGGCCCGACGGCACACCTACGTTACCGTGTCTCAAGTCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCTCCGCTGGCCAAATGTGTGCGAGCGGGACGGGGCGAGTACCTCTGTGAGCCACCAATTTATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTACAGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGTGGGCTTCTTCTTCTCATCTGGTGGTGGCGGCTGTGACGCTCTGCCGCTG
CGCAGCCCCCAAGAAAGGCTGGGCTCCCCACCCTGCACAAGATCTCCGCTTCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGGCATCGCAAGGCTGTCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCAATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTGCGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAACATCATCAACCTGCTGGGCGCTGCACGCAGGGCGGGCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGCCCCGGGCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCTGTGCTTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCAGAG
AGTGCATCCACAGGGACCTGGCTGCCCCGAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGGACGTGCAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTGTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCTTTGGGGTCTGCTCTGGGAGATCTTCACGCTGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTTTCAAGTGTCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGACACACGACCTGTACATGATCATGCGGGAGTGTGGCATGCCGCGCCCTCCAGAGGCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCTTACCCTGACGTCCACCGACGAGTACCTGGACCTGTGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCAGCTCCAGCTCTCAGGGGACGACTCCGTGTTTGGCCACGACCTGCTGCCCCCGGCCCA
CCAGCAGTGGGGGCTCGCGGACGCGA

Figure 2M

Mutant X909L FGFR3-IIib:

ATGGGCGCCCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAAGTCCCGGGCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGGCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCGCGGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGCCCATCCTGCAGSCGGGGCTGCCGGCCAACAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCACCTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGGCCCGGACGGCACACCTACGTTACCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCTGGCCAATGTGTGCGAGCGGGACGGGGGGCGAGTACCTCTGTGAGCCACCAATTTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCTGTTCATCTGGTGGTGGCGGCTGTGACGCTCTGCCGCTG
CGCAGCCCCCACAAGAAAGGCCTGGGCTCCCCCACCCTGCACAAGATCTCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGGCATCGCAAGGCTGTCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCTGGGCAAGCCCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTACCCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCCGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGGCCCCGGGCTGGACTACTCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCTGTGCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCCGAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCAGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTGTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCTTTGGGGTCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCAGAGGGCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTGCGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGGCCACGACCTGCTGCCCCGGCCCCA
CCAGCAGTGGGGGCTCGCGGACGTTA

Figure 2N Mutant 1

Mutant N542K FGFR3-IIIb:

ATGGGCGCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGCGCCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCTGTGGGCGAGCGGCAGAAAGTCCCGGGCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCAGCGAGCGCTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGGCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCGCGGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGGCCCTCGGACCGCGGCAACTACACCTGCGTCTGGAGAACAAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGACCCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCCGACGGCACACCCCTACGTTACCGTGCTCAAGTCTTGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCTGGCCAATGTGTCGGAGCGGGACGGGGCGAGTACCTCTGTGAGCCACCAATTTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCTGTTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCTG
CGCAGCCCCCAAGAAAGGCCTGGGCTCCCCACCGTGCACAAGATCTCCCGCTTCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCATCGCAAGGCTGTCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCGAGCTCGAGCTGCTGCCGACCCCAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCAAGCCTGTACCCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAAAGTGTGGGCGCCTGCACGAGGGCGGGCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGGCCCCCGGGCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCTGTGCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCTTTGGGGTCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCAGAGGCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTGCGCGCCTTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCAAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGGCCACGACCTGCTGCCCCGGCCCCA
CCAGCAGTGGGGCTCGCGGACGTGA

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Figure 20 Mutant 2

Mutant N542K EGFR3-IIIb:

ATGGGCGCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCCTGGCCATCCTGGCCGGCGCCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCTGTGGGGCGAGCGGCAGAAAGTCCCGGGCCAGAGCCCGGCCAGCAGGAGCACTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGGCCCTCGGAGCGTGTCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCTTACTGGACACGGGCCGAGCGGATGGAC
AAGAAGCTGCTGGCGGTGCCGGCCGCCAACCCGTCCGCTTCCGCTGCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCGCGGGCAGCACCCGATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGGCTCGGACCGCGGCAACTACACCTGCGTGGTGGAGAACAAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGACCGCGCCCATCTGCAGGCGGGGCTGCCGGCCAAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCTACTGCAAGGTGTACAGTGACGCACAGCCCAACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGGCCCGACGGCACACCCCTACGTTACCGTGCTCAAGTCTGGATCAGTGAGAGTGTGGAGGGCGAC
GTGCGCCTCCGCTGGCCATGTGTGGAGCGGGACGGGGGCGAGTACCTCTGTGAGCCACCAATTTTCATAGGCGTGGC
CGAGAAGGCCCTTTGGCTGAGCGTTACCGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCTGTTTCATCTGGTGGTGGCGGCTGTGACGCTCTGCCGCTG
CGCAGCCCCCAAGAAAGGCCTGGGCTCCCCCACCCTGCACAAGATCTCCGCTTCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGGCATCGCAAGGCTGTCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCCTGCCGACCCCAATGGGAGCTGTCTCGGGCCCGGCTGACCCCTGGGCAAGCCCTT
GGGGAGGCTGCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTACCCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTGCGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAACATCATCAAGCTGCTGGGGCGCTGCACGCGAGGGCGGGCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGGCGCCCCGGGCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCTGTGCTACAGGTGGCCCCGGGCATGGAGTACTTGGCCTCCACAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAAAGTGTGAAGATCGCAGACTTCGGGCTG
GCCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGCTGCCCGTGAAGTGGATGGCGCTGAGGC
CTTGTGTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCTTTGGGGTCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCCCAAC
TGACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCAGAGGCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTGCGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCAAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGGCCAGACCTGCTGCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGTGA

Figure 2P Mutant 1

Mutant G382R FGFR3-IIIb:

ATGGGCGCCCCTGCCTGCGCCCTCGCGCTCTGCGTGCCCGTGCCCATCGTGCCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAAGTCCCGGGCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCGCCCCGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCACGAGGACTCCGGGGCCTA
CAGCTGCCCGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGGCCCTTACTGGACACGGCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCAGCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCTCGGACCGCGGCACTACACCTGCGTCTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGTCCCCGACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTACGACACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCGGACGGCACACCTACGTTACCGTGCTCAAGTCTTGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCTGGCCAATGTGTGGAGCGGGACGGGGCGAGTACCTCTGTGAGCCACCAATTTATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGACAGGCATCCTCAGCTACAGGCTGGGCTTCTTCTGTTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCTG
CGCAGCCCCCCCCAAGAAAGGCCTGGGCTCCCCCACCCTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGGCATCGCAAGGCTGTCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAATGGGAGCTGTCTCGGGCCCGGCTGACCTGGGCAAGCCCCCT
GGGGAGGGCTGCTTCGGCCAGGTGGTTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGCGGGCCCCGGGCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCTGTGCTTACCAGGTGGCCCGGGGCATGGAGTACTTGGCTCCCAGA
AGTGCATCCACAGGGACCTGGCTGCGCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCCGGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCCGCTGCCCGTGAAGTGGATGGCGCTGAGGC
CTTGTTTGACCGAGTCTACACTACCCAGAGTGACGTCTGGTCTTTGGGGTCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGTGGCATGCCGCGCCCTCCAGAGGCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCTTACCCTGACGTCCACCGACGAGTACCTGGACCTGTGCGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCGAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGGCCACGACCTGCTGCCCCGGCCCCA
CCCAGCAGTGGGGGCTCGCGGACGTGA

Figure 2Q Mutant 2

Mutant G382R FGFR3-IIIB:

ATGGGCGCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCTCGTGGGGCGAGCGGCAGAAAGTCCCGGGCCAGAGCCCGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCTGGTGGGGCCCCAGCGGCTGCGAGTGTGAATGCCTCCACAGGAGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGGCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCAACACCGTCCGCTTCCGCTGCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGCGCAGCACCGCATTGAGGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCCAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCAGCTGGAGGTGA
ACGGCAGCAAGGTGGGCCCCGACGGCACACCCCTACGTTACCGTGCTCAAGTCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCTGGCCAATGTGTGCGAGCGGGACGGGGCGAGTACCTCTGTCGAGCCACCAATTTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTACGGGCCCCGAGCAGCCGAGGAGGAGTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACCGGGTGGGCTTCTTCTGTTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCTG
CGCAGCCCCCAAGAAAGGCTGGGCTCCCCACCGTGCAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACCGCTCCATGAGCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCTCAGGGGAGGGCCCCCAGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCTT
GGGGAGGGTGTCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCAAGCCTGTACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTGCGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGCGGGCCCCCGGGCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCTGTGCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCCGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGCGCGGCTGCCCGTGAAGTGGATGGCGCTGAGGC
CTTGTTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCTTTGGGGTCTGCTCTGGGAGATCTTCACGCTGGGG
GCTCCCCGTACCCCGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCAGAGGGCCACCTTCAAGCAGCTGGT
GGAGGACCTSGACCGTGTCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTGCGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACCCCCAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGGCCACGACCTGCTGCCCCGGCCCCA
CCAGCAGTGGGGGCTCGCGGACGTGA

Figure 2R

Mutant G377C FGFR3-IIb:

ATGGGCGCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAAGTCCCGGGCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCGCCCCGGGGTGGTCCCATGGGGCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGGCCCTTACTGGACAGGGCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCAACACCGTCCGCTTCCGCTGCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCCGCGGCGAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCCTCGGACCGCGGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCAACCGGCCCATCCTGCAGGCGGGGGTCCCGGCCAACCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCCACTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGGCCGGACGGCACACCTACGTTACCGTGCTCAAGTCCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCTGGCCAAATGTGTGCGAGCGGGACGGGGGCGAGTACCTCTGTGAGCCACCAATTTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTACGGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCATGCATCCTCAGCTACGGGGTGGGCTTCTTCTGTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCTG
CGCAGCCCCCAAGAAAGGCTGGGCTCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGCGCATCGCAAGGCTGTCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCCTGGGCAAGCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCAAGCCTGTACCCTG
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTGCGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCCTGCACGCAGGGCGGGCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGGCCCCCGGGCTGGACTACTCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCTGTGCCTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCGAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCCGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTGTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCTTTGGGGTCTGCTCTGGGAGATCTTCACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGTGGCATGCCGCGCCCTCCAGAGGGCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTGCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCAAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTTGGCCACGACCTGCTGCCCCGGCCCCA
CCAGCAGTGGGGGCTCGCGGACGTGA

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Figure 25

Mutant A393E FGFR3-IIIb:

ATGGGCGCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCTGTGGGGCGAGCGGCAGAAAGTCCCGGGCCAGAGCCCGGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCGCCCCGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCACAGGG
CTGGTGCCCTCGGAGCGTGTCTGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCACGAGGACTCCGGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCGTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCCGGCCGCCAACACCGTCCGCTTCCGCTGCCAGCCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCGCGGGCAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TACGGAAGCGTGGTGCCTCGGACCGCGCAACTACACCTGCGTCGTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCCGCAACCGGCCATCCTGCAGGCGGGGCTGCCGGCCAACAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCACCTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGCCCCGGACGGCACACCTACGTTACCGTGCTCAAGTCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCCTGGCCAATGTGTCGGAGCGGGACGGGGCGAGTACCTCTGTCGAGCCACCAATTTATAGGCGTGCC
CGAGAAGGCCTTTTGGCTGAGCGTTACGGGGCCCCGAGCAGCCGAGGAGGAGCTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCTGTTTCATCCTGGTGGTGGAGGCTGTGACGCTCTGCCGCTG
CGCAGCCCCCAAGAAAGGCCTGGGCTCCCCACCGTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACGCGTCCATGAGCTCCAACACACCACTGGTGGCATCGCAAGGCTGTCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCCAATGGGAGCTGTCTCGGGCCCGCTGACCCTGGGCAAGCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCCAAGCCTGTACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTCGGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAAACATCATCAACCTGCTGGGCGCCTGCACGAGGGCGGGCCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGGCCCCCGGGCTGGACTACTCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCTGTGCTTACCAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCAGA
AGTGCATCCACAGGGACCTGGCTGCCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCCGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTGTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCTTTGGGGTCTGCTCTGGGAGATCTTCACGCTGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCAGAGGCCACCTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTGCGGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCAAGCTCCAGCTCCTCAGGGGACGACTCCGTGTTGCCACGACCTGCTGCCCCGGCCCCA
CCAGCAGTGGGGGCTCGCGGACGTGA

Figure 2T

Mutant P250R FGFR3-IIIb:

ATGGGGCGCCCTGCCTGCGCCCTCGCGCTCTGCGTGGCCGTGGCCATCGTGGCCGGCGCCTCCTCGGAGTCCTTGGGGAC
GGAGCAGCGCGTCGTGGGGCGAGCGGCAGAAGTCCCGGGCCAGAGCCCGCCAGCAGGAGCAGTTGGTCTTCGGCAGCG
GGGATGCTGTGGAGCTGAGCTGTCCCCCGCCCGGGGGTGGTCCCATGGGGCCCACTGTCTGGGTCAAGGATGGCAGAGG
CTGGTGGCCTCGGAGCGTGTCTGGTGGGGCCCCAGCGGCTGCAGGTGCTGAATGCCTCCACAGGAGTCCCGGGCCTA
CAGCTGCCGGCAGCGGCTCACGCAGCGCTACTGTGCCACTTCAGTGTGCGGGTGACAGACGCTCCATCCTCGGGAGATG
ACGAAGACGGGGAGGACGAGGCTGAGGACACAGGTGTGGACACAGGGGCCCCCTTACTGGACACGGCCCGAGCGGATGGAC
AAGAAGCTGCTGGCCGTGCGGGCCGCAACACCGTCCGCTTCCGCTGCCAGCGCTGGCAACCCCACTCCCTCCATCTC
CTGGCTGAAGAACGGCAGGGAGTTCGCGGGCAGCACCGCATTGGAGGCATCAAGCTGCGGCATCAGCAGTGGAGCCTGG
TCATGGAAAGCGTGGTGCCTCGGACCGGGCAACTACACCTGCGTCTGGAGAACAAGTTTGGCAGCATCCGGCAGACG
TACACGCTGGACGTGCTGGAGCGCTCCCGGCACCGGCCCATCCTGCAGGCGGGGCTGCCGGCAACCCAGACGGCGGTGCT
GGGCAGCGACGTGGAGTTCACCTGCAAGGTGTACAGTGACGCACAGCCCCACATCCAGTGGCTCAAGCACGTGGAGGTGA
ACGGCAGCAAGGTGGGCCCGGACGGCACACCTACGTTACCGTGCTCAAGTCTGGATCAGTGAGAGTGTGGAGGCCGAC
GTGCGCCTCCGCCTGGCCAATGTGTGCGAGCGGGACGGGGCGAGTACCTCTGTGAGCCACCAATTTTCATAGGCGTGGC
CGAGAAGGCCTTTTGGCTGAGCGTTCACGGGCCCCGAGCAGCCGAGGAGGAGTGGTGGAGGCTGACGAGGCGGGCAGTG
TGTATGCAGGCATCCTCAGCTACGGGGTGGGCTTCTTCTGTTTCATCCTGGTGGTGGCGGCTGTGACGCTCTGCCGCCTG
CGCAGCCCCCAAGAAAGGCCTGGGCTCCCCCACCCTGCACAAGATCTCCCGCTTCCCGCTCAAGCGACAGGTGTCCCT
GGAGTCCAACCGCTCCATGAGCTCCAACACACCACTGGTGGCATCGCAAGGCTGTCTCAGGGGAGGGCCCCACGCTGG
CCAATGTCTCCGAGCTCGAGCTGCCTGCCGACCCAAATGGGAGCTGTCTCGGGCCCGGCTGACCTGGGCAAGCCCCCTT
GGGGAGGGCTGCTTCGGCCAGGTGGTTCATGGCGGAGGCCATCGGCATTGACAAGGACCGGGCCGCAAGCCTGTACCGT
AGCCGTGAAGATGCTGAAAGACGATGCCACTGACAAGGACCTGTGCGACCTGGTGTCTGAGATGGAGATGATGAAGATGA
TCGGGAAACACAAAACATCATCAACTGCTGGCGCCTGCACGCAGGGCGGGCCCCCTGTACGTGCTGGTGGAGTACGCG
GCCAAGGGTAACCTGCGGGAGTTTCTGCGGGCGCGGGCCCCCGGGCCTGGACTACTCCTTCGACACCTGCAAGCCGCC
CGAGGAGCAGCTCACCTTCAAGGACCTGGTGTCTGTGCTACAGGTGGCCCGGGGCATGGAGTACTTGGCCTCCCAGA
AGTGATCCACAGGGACCTGGCTGCCGCAATGTGCTGGTGACCGAGGACAACGTGATGAAGATCGCAGACTTCGGGCTG
GCCCCGGACGTGCACAACCTCGACTACTACAAGAAGACAACCAACGGCCGGCTGCCCGTGAAGTGGATGGCGCCTGAGGC
CTTGTTTGACCGAGTCTACACTCACCAGAGTGACGTCTGGTCTTTGGGGTCTGCTCTGGGAGATCTTACGCTGGGGG
GCTCCCCGTACCCCGGCATCCCTGTGGAGGAGCTCTTCAAGCTGCTGAAGGAGGGCCACCGCATGGACAAGCCCGCCAAC
TGCACACACGACCTGTACATGATCATGCGGGAGTGCTGGCATGCCGCGCCCTCCAGAGGCCCACTTCAAGCAGCTGGT
GGAGGACCTGGACCGTGTCTTACCGTGACGTCCACCGACGAGTACCTGGACCTGTGCGCGCCTTTCGAGCAGTACTCCC
CGGGTGGCCAGGACACCCCAAGCTCCAGCTCCTCAGGGACGACTCCGTGTTGCCACGACCTGCTGCCCCGGCCCCA
CCCAGCAGTGGGGCTCGCGGACGTGA

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FIGURE 3

